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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/650,507	08/27/2003	Bernard Bihain	G-029US05DIV	6971

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EXAMINER	
O'HARA, EILEEN B	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/650,507	BIHAIN ET AL.	
	Examiner	Art Unit	
	Eileen B. O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *4-9,13-18 and 36-45* is/are withdrawn from consideration.

5)☒ Claim(s) *2,10,11,19-24,32 and 34* is/are allowed.

6)☒ Claim(s) *1, 3, 12, 25-31, 33 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-45* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/269,939.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/26/04 & 4/29/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-45 are pending in the instant application.

Election/Restrictions

2. Applicant's election without traverse of Group I (claims 1-3, 10-12 and 19-35) in the reply filed on June 1, 2006 is acknowledged.

Claims 4-9, 13-18 and 36-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-3, 10-12 and 19-35 are currently under examination.

Specification

3.1 The disclosure is objected to because of the following informalities: on page 56, first line, the brackets ( ) after "β plasmid is blank and should have a filled circle.

Appropriate correction is required.

3.2 The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4.1 Claims 1, 3, 12, 25-31, 33 and 35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification describes a polypeptide sequence consisting of SEQ ID NO: 8 (α subunit), which is shown to have the following activities (when present in the LSR receptor complex also comprising other polypeptides: binding and internalizing lipoproteins and binding and internalizing leptin. However, the claims as written include polypeptides comprising fragments and encompass polypeptides that vary substantially in length and also in amino acid composition. The instant disclosure of a single polypeptide, that of SEQ ID NO: 8 with the instantly disclosed specific activities, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. The claims as written encompass a polypeptide comprising either 10 to 15 consecutive amino acids of SEQ ID NO: 8 or a biologically active fragment of the polypeptide of SEQ ID NO: 8 as recited in claims 3 or 12. The specification on pages 22-23 defines biologically active fragments as an amino acid sequence exhibiting at least one of the LSR receptor activities, and Table 4 identifies specific portions of the protein having potential domains or motifs. A genus claim may be supported by a representative number of species as set

forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

Analogously, a description of a genus of polypeptides may be achieved by means of a recitation of a representative number of polypeptides, defined by amino acid sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, the polypeptide sequence SEQ ID NO: 8 and two other human sequences which are identical except for lacking a portion of SEQ ID NO: 8 internally (Figure 3). Given the fact that the specification fails to provide objective evidence that the additional sequences are indeed

species of the claimed genus it cannot be established that a representative number of species have been disclosed to support the genus claim. No specific activity is set forth for the additional sequences. There is no correlation or nexus provided between possession of these additional sequences and the encompassed functional features of SEQ ID NO: 8 such that it is clearly conveyed that possession of any polypeptide having this structural region in common would possess these functional features.

4.2 Claims 1, 3, 12, 25-31, 33 and 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using a polypeptide comprising the amino acid sequence of SEQ ID NO: 8 (LSR α subunit), does not reasonably provide enablement for making and using a polypeptide comprising fragments or polypeptides that vary substantially in length and also in amino acid composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant specification discloses a naturally occurring human polypeptide comprising the amino acid sequence presented in SEQ ID NO: 8. This protein has been demonstrated to be a LSR α subunit, and apparently functions in binding and internalizing lipoproteins and binding and internalizing leptin. However, because these claims encompass a polypeptide that comprises a biologically active fragment of the polypeptide of SEQ ID NO: 8, for example a fragment comprising from 10 to 15 consecutive amino acids or a biologically active fragment of the polypeptide of SEQ ID NO: 8 as recited in claims 3 or 12, a practitioner can not make a protein comprising a biologically active fragment, other than the ones disclosed in the instant specification, and expect it to have the same functions of binding and internalizing lipoproteins

and binding and internalizing leptin. As claimed, such a polypeptide may only comprise one of the disclosed biologically active fragments, and the rest of the polypeptide may be completely different. The disclosure of three LSR subunits with natural amino acid sequences is clearly insufficient support under the first paragraph of 35 U.S.C. § 112 for claims which encompass a protein comprising such a biological fragment. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even the disclosure of a region of specific biological activity may not be sufficient, as the ordinary artisan would immediately recognize that an active or

binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. For example, Transforming Growth Factor (TGF-beta) Family OP-1 induces metanephrongenesis whereas closely related TGF-beta family members-BMP-2 and TGF-beta1-have no effect on metanephrogenesis under identical conditions (Vukicevic et al., 1996, PNAS USA 93:9021-9026). Platelet-derived Growth Factor (PDGF) Family VEGF, a member of the PDGF family, is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells while PDGF is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (Tischer et al., U.S. Patent 5,194,596, column 2, line 46 to column 3, line 2). Finally, vertebrate growth hormone of 198 amino acids becomes an antagonist (inhibitor of growth) when a single amino acid is changed (Kopchick et al, U.S. Patent No. 5,350,836). Even 99% homology does not allow predictability in this instance. Given the unpredictability of homology comparisons, and the fact that the specification fails to provide objective evidence that the additional sequences are indeed species of the claimed genus it cannot be established that a representative number of species have been disclosed to support the genus claim.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of

experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

For the reasons discussed above, due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which only require the presence of one biologically active fragment, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Steingrimsson et al., Database UniProt_7.2, Accession No. Q61148, Nov. 1, 1996, (cited by Applicants, see enclosed sequence alignment).

Claim 1 encompasses as purified or recombinant Lipolysis Stimulated Receptor, wherein said receptor comprises a polypeptide comprising at least 10 to 15 consecutive amino acids of SEQ ID NO: 8.

The recombinant polypeptide of Steingrimsson et al., Accession No. Q61148 comprises an amino acid fragment that is 100% identical to several stretches of the polypeptide of SEQ ID NO: 8 and comprising more than 10 to 15 consecutive amino acids. Therefore, the polypeptide meets the limitations of the claim.

Conclusion

6.1 Claims 2, 10, 11, 19-24, 32 and 34 are allowed.

6.2 Claims 1, 3, 12, 25-31, 33 and 35 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nichol can be reached at (571) 272-0835.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner